A FACILE SYNTHESIS OF 4,4-BIS(TRIFLUOROMETHYL)-IMIDAZOLINES*VIA* A NOVEL OXIDATIVE IMIDAZOLE REARRANGEMENT[1]

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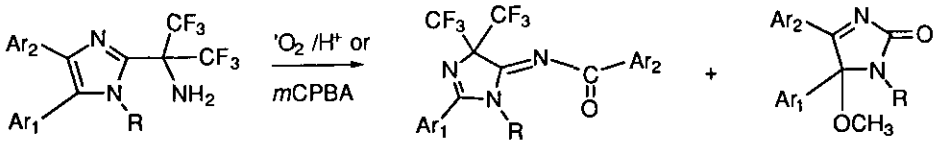
Abstract - Oxidation of imidazole (**1**) with singlet oxygen or *m*-chloroperbenzoic acid affords novel 4,4-bis(trifluoromethyl)imidazolines in high yield *via* a unique oxidative ring opening and subsequent acid catalyzed dehydrocyclization.

Trifluoromethyl-substituted heterocyclic compounds have a wide range of biological activities,[4,5] yet these compounds remain synthetically challenging. Several 4,4-bis(trifluoromethyl)imidazolines are potent CNS agents,[6] antiinflammatory agents[7] and angiotensin II receptor antagonists.[8] Recently, they were also identified as potent ACAT inhibitors and cholesterol biosynthesis inhibitors and have potential for treatment of atherosclerosis and hypocholesterolemia.[9] We report here a unique oxidative imidazole ring opening by singlet oxygen or *m*-chloroperbenzoic acid (*m*CPBA) and then a facile acid catalyzed dehydrocyclization process to convert readily available imidazoles to 4,4-bis(trifluoromethyl)imidazolines.



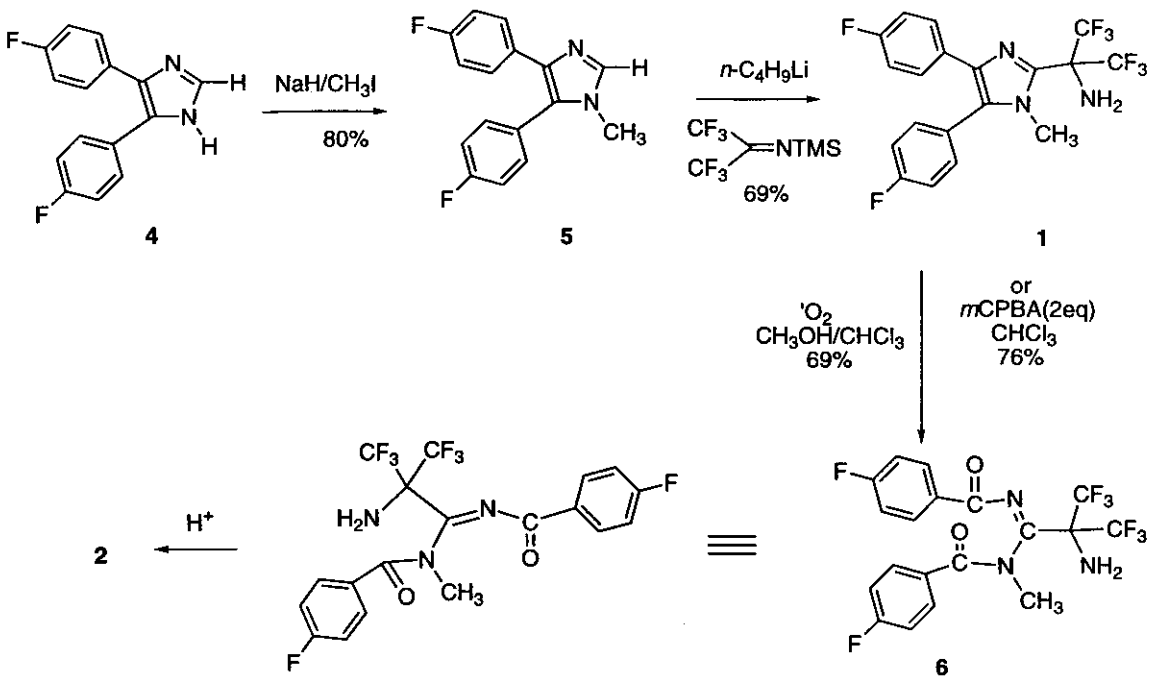
1 **2** **3**

Ar_1=Ar_2=*p*-F-Ph
R=CH_3

Imidazole (**4**) was prepared according to literature procedure[10] from DL-difluorobenzoin.[11] Alkylation of **4** with NaH/MeI gave **5** in 80% yield. Lithiation of **5** with *n*-BuLi followed by addition of $(CF_3)_2C$=NTMS[12] gave **1** in 69% yield. Treatment of **1** with singlet oxygen, generated from a 400 watt tungsten lamp with methylene blue as a sensitizer, gave rise to **6** within 1 h in $CHCl_3$ and methanol (1:1). Treatment of the solution of **6** obtained above with a 1N HCl ether solution afforded the cyclized product (**2**), which was obtained in 69% along with about 6% of **3** after flash column chromatography. Intermediate (**6**) was not very stable. It cyclizes to **2** spontaneously on silica gel on attempts to purify and

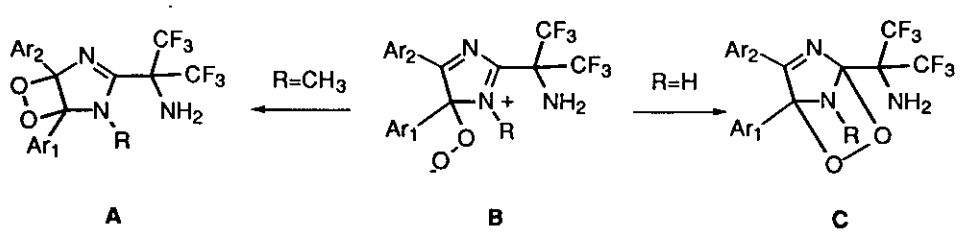
characterize it. The singlet oxygen ring opening took as long as 8 h when 150 watt tungsten lamp was used. Alternatively, **1** could be oxidized with *m*CPBA in refluxing chloroform to give the same intermediate (**6**), which spontaneously cyclized to **2** in 76% yield (**Scheme 1**).

Scheme 1

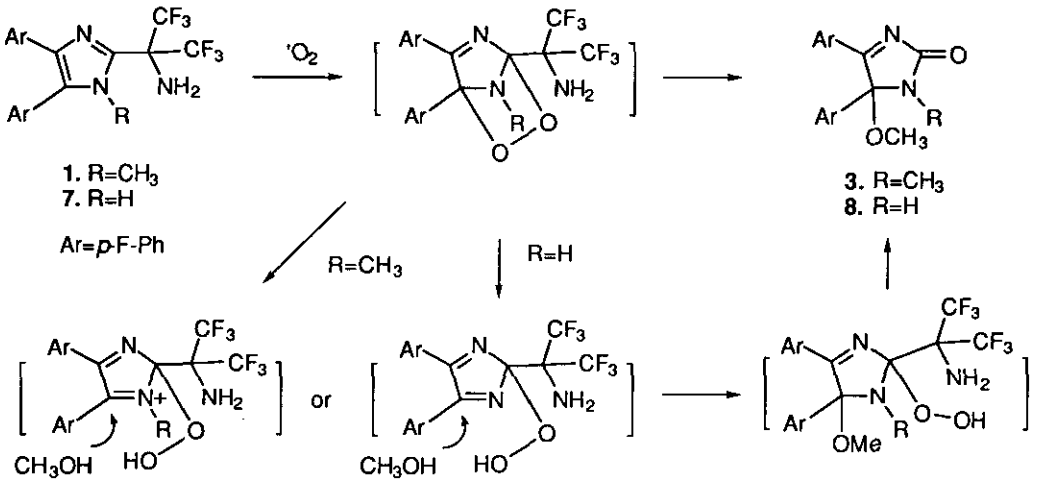


Singlet oxygen oxidation of imidazole has low selectivity in general. The singlet oxygen can add to the imidazole ring in 1,2 addition fashion to form a dioxetane (**A**), or 1,4 addition fashion to form an endoperoxide (**C**), presumably *via* a common zwitterion (**B**) (**Scheme 2**).[13] The photooxidation of imidazole has been studied extensively and low chemoselectivity and chemical yield were observed in most cases.[14] *N*-1 substituted imidazole should form dioxetane (**A**) rather than endoperoxide (**C**) due to the steric effect of *N*-substitution. On the other hand, *N*-1 non-substituted imidazole (R=H) should give endoperoxide (**C**) or both (**A**) and (**C**). Indeed, photooxidation of **7** gave **8** as a major product in 42% yield and no ring openned dibenzoylamidine or cyclized imidazoline product was observed (**Scheme 3**).

Scheme 2

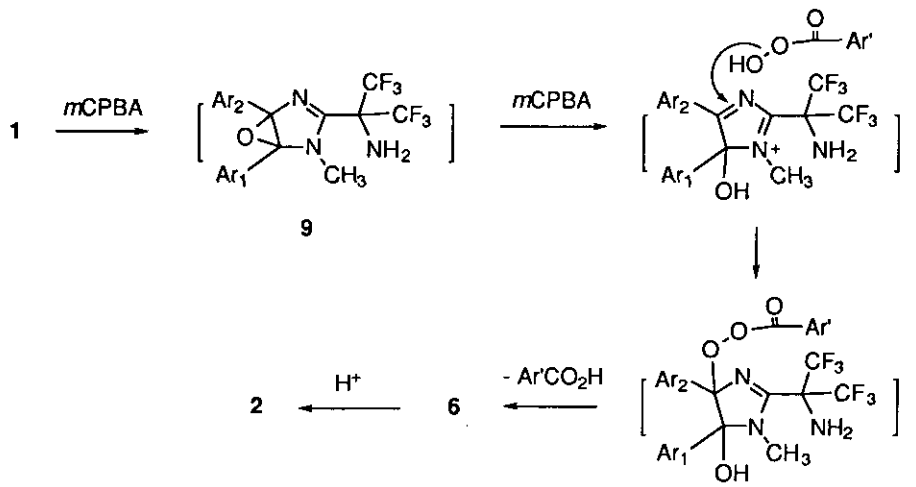


Scheme 3



We were very surprised that oxidation of imidazole **1** with *m*CPBA gave the same product as photooxidation's. There have been few reports on oxidative cleavage of heterocycles, such as benzofurans, tetrahydrobenzofurans[15,16], and pyridone[17] by *m*CPBA. This is the first oxidative cleavage of imidazole by *m*CPBA to our knowledge. It presumably goes through an epoxide intermediate **9** followed by further rearrangement as shown in **Scheme 4**. The acidic reaction medium cyclizes **6** as soon as it is formed.

Scheme 4



The structure of **2** and **3** was determined by analyzing all spectra data (^{1}H-nmr, ^{13}C-nmr, ^{19}F-nmr, ir, uv, and ms). **2** was also confirmed by X-ray (**Figure 1**). *p*-F substitution is particularly attractive to us because fluorine can be displaced by a variety of nucleophiles, thus providing a quick access to a series of new analogs for biological testing. **2** has an IC_{50} 20μM as an ACAT inhibitor and an IC_{50} 2.5μM as a HMG-CoA reductase inhibitor.

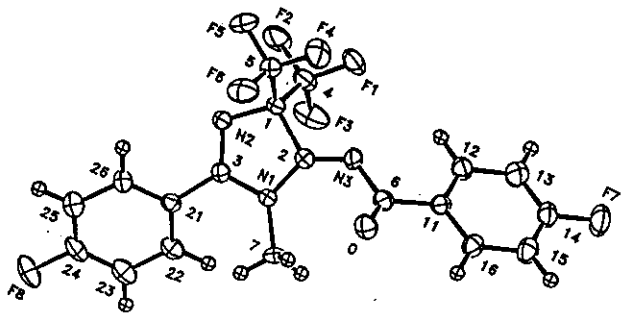


Figure 1

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REFERENCES AND NOTES

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